Multiple sclerosis

Calcium antagonists in exercise-induced asthma

SIR,—The report by Dr K R Patel (21 March, p 932) that the calcium antagonist verapamil inhibits exercise-induced asthma is supported by the observations of Cerrina and co-workers,[1] who report that nifedipine, another antagonist of calcium influx, also prevents the bronchoconstrictor response to exercise in asthmatics. In discussing the mechanism of exercise-induced asthma both Dr Patel and Cerrina *et al* suggest that the release of spasmogens from lung mast cells may play a role in this condition and that calcium antagonists, in addition to relaxing smooth muscle, may prevent exercise-induced bronchospasm by inhibiting the calcium-dependent release of these spasmogens.

In recent studies on the antigen-induced release of spasmogens from sensitised fragments of human lung, using well-established techniques,[2] we have confirmed that there is an absolute requirement for extracellular calcium ions in the release processes. However, nifedipine and verapamil at concentrations up to 100 μmol/l failed to inhibit the release of histamine from human lung when the drug was preincubated with the tissue for 30 minutes before challenge. We did observe, however, that verapamil at 100 μmol/l, but not at 10 μmol/l, inhibited the release of slow-reacting substance. In addition, verapamil (500 pmol/l-150 μmol/l) inhibited the spasmogenic effect of histamine (1 μg/ml) on human superfused bronchial smooth muscle with a concentration effective in 50% of cases (EC_{50}) of 9 μmol/l.

Spasmogens derived from mast cells are unlikely to make a major contribution to the bronchoconstrictor response to exercise in asthmatics.[3] Even if their contribution is greater than currently believed the results presented here suggest that calcium antagonists exert their inhibitory effects in exercise-induced asthma on the constrictor responses of bronchial smooth muscle rather than on the release of spasmogens from mast cells.

Nifedipine was a gift from Bayer UK Limited and verapamil was a gift from Abbott Laboratories Limited.

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[2] Butchers PR, Fullarton JR, Skidmore IF, Thompson LE, Vardey CJ, Wheeldon A. *Br J Pharmacol* 1979;**67**:23-32.
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Are fibre supplements really necessary in diverticular disease of the colon?

SIR,—What should we do when clinical impressions over a number of years are not confirmed by a randomised, cross-over, double-blind controlled trial? With only an occasional exception patients with symptomatic uncomplicated diverticular disease of the colon report a persisting improvement when they take extra dietary fibre, often without an additional bulking agent. Personally I accept the verdict of my patients and then look doubly carefully at the double-blind trial.

The trial which you report by Mr M H Ornstein and others (25 April, p 1353) surely has an obvious fallacy. I was taught that the dose of a drug is that which has the desired effect without causing side effects, and the same is true for dietary supplements. To give a standard amount, and a small one at that, to every patient irrespective of their real need invites statistical disaster. In their subsequent letter (16 May, p 1629) the authors admit that "it is important to give sufficient bran or ispaghula to relieve straining and the amount will vary greatly between patients." This is equally true for other symptoms. With their own words they themselves condemn their own trial, which I believe is meaningless and dangerously misleading, although it appears to be beautifully designed and executed.

I am not alone in thinking that this paper should have been published in a specialist and not a leading world medical journal. This is not the first time that a clinical trial has given a dubious answer and I greatly welcome the article in your new series "Statistics in Question" about assessing clinical trials (16 May, p 1605).

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SIR,—It is regrettable that Mr M H Ornstein and others (25 April, p 1353), after carrying out an extensive clinical trial, have subsequently appeared to misinterpret their results. They have demonstrated that increasing the fibre intake of their patients with diverticular disease by 4·6 g was inadequate to produce sufficient relief of symptoms to reach levels of statistical significance, although the lowest mean symptom scores for pain, bowel symptoms, and general symptoms were seen when patients were taking bran. An increase of mean stool weight of less than 20 g daily and an increase in stool frequency from 9·55 to 10·34 per week may be inadequate to produce the desired effect on colonic behaviour.

I have found in clinical practice that symptomatic relief in diverticular disease is best achieved by increasing fibre intake by 20 g. This more than doubles the total fibre intake of most patients and almost invariably has a marked effect on bowel habit. Although patients will tolerate only a limited amount of bran, as Mr Ornstein and others state (16 May, p 1629), they will tolerate a much greater increase in fibre intake in the form of wholemeal bread, high-fibre breakfast cereals, etc.

A direct comparison has been made between this trial and a similar trial in Oxford.[1] The differences in results are difficult to explain, but could have been due to differences in the patients selected for the trials. Those at Oxford were all suffering from severe symptoms and all had abdominal pain in addition to bowel symptoms. The initial fibre intake of the patients may have been different. Differences in scoring techniques may have been important in the assessment of true differences in scores. In the previous trial a cross-over design was deliberately not used. The effect of altering fibre intake on bowel behaviour may persist for some months, in which case cross-over studies are inappropriate.

In the Oxford trial patients took the crispbread instead of bread, so that the placebo group had no increase in their normal fibre intake. In the present trial the control group did, in fact, have an increased fibre intake, according to Mr Ornstein and his colleagues (p 1629), and it could be argued that there was no valid control group—only three different treatment groups.

The main value of this study has been to emphasise that small differences in fibre intake (equivalent to a small 50-g (1¾-oz) packet of peanuts daily) may not be effective in treating diverticular disease. The recommended intake of many proprietary "bran" preparations is totally inadequate. Many gastroenterological and surgical clinics have found that a high-fibre diet (that is, 40 g a day—not 22 g as in this study) is effective in treating diverticular disease, but the optimal increase in dietary fibre required remains to be established scientifically.

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[1] Brodribb AJM. *Lancet* 1977;i:664-6.

SIR,—Despite the spirited criticism of Dr J R Thornton, Mr R T Burkitt, and Dr K O A Vickery (9 May, p 1546), it was unrealistic to have expected Mr M H Ornstein and his colleagues to retract the conclusions of their paper (25 April, p 1353)—namely, that dietary fibre supplements "do no more than relieve constipation" and "are unnecessary in the long-term management of uncomplicated diverticular disease." As it stands, however, their paper will undoubtedly be misquoted as its finer points become clouded by the passage of time. It is simply not enough for the authors to suggest subsequently (16 May, p 1629) that they made no claims concerning prevention of the disease; the fact that they neither mentioned this in their paper nor pointed out the total lack of other trial data relating to prophylaxis represents an important omission from their original and otherwise useful contribution.

Mr Ornstein and his colleagues are quite right in saying that a trial to test the lifelong prophylactic effect of fibre is impossible; a more realistic yet equally important question and, incidentally, one which they are in a prime position to tackle is: "Do fibre supplements, when given *long term* to patients with uncomplicated diverticular disease, prevent progression to the more serious stages of this common condition?" If the trial is explained, patients' co-operation should be no more of a problem in a trial to answer this question than, say, in a trial of antihypertensive therapy in the prevention of myocardial infarction or stroke.

It is a shame that the *Index Medicus* does not link original papers with the correspondence that they generate, for this might help to rectify sweeping overstatement by authors and prevent uncritical overinterpretation by readers. This paper and the constructive ensuing debate are a fair example of this problem.

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Multiple sclerosis

SIR,—Your leading article on multiple sclerosis (14 February, p 502) suggests that in a cross-sectional survey the median duration of the disease can be calculated by doubling the time from onset to prevalence day. The fallacy of this statement can be demonstrated with an extreme but simple example.

Suppose that 80% of patients with a particular disease survive for six months after

onset, while the remaining 20% survive for six years. Then a cross-sectional study can be expected to contain 25% short-term survivors and 75% long-term survivors, because of the greater risk of short-term survivors being dead before "prevalence day." Thus, assuming a stable population and incidence, we can expect a median interval from onset to prevalence day of two years. The recommended method would therefore estimate the median survival to be four years compared to the true figure of six months.

It is also apparent from this example that an increase in estimated median survival can result from a shortening of life expectancy among those with a poor prognosis.

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**Poskanzer *et al*[1] point out (p 236) the statistical problem: "Assuming that there is no change in the pattern of a disease, average duration could be estimated as twice the period from onset to prevalence day. It is therefore assumed that the duration among a group of patients identified on prevalence day will approximate to a normal distribution and that ascertainment of nearly all existing cases will be achieved, especially those cases with a recent onset of the disease. The latter requirement has probably not been fully met in each of the four surveys in the Orkneys and Shetlands. However, the method can be applied by using information discovered later about cases with onset close to prevalence day. The effect of not identifying all cases with recent onset overestimates the average duration. If it is assumed, however, that the error resulting from the exclusion of recent-onset cases is relatively constant over the four surveys, the data can be used to determine if the duration has changed over time but not to determine the actual duration of the disease." Space did not allow us to go into these details about the statistical method in our leading article, but we are grateful to Dr Prescott for writing.—ED, *BMJ*.

[1] Poskanzer DC, Prenney LB, Sheridan JL, Yon Kondy J. *J Epidemiol Community Health* 1980;**34**:229-39.

Trial of folate treatment to prevent recurrence of neural tube defects

SIR,—We have been extremely interested to read the recent papers by Dr K M Laurence and others (13 December, p 1592; 9 May, p 1509) on the relationship of maternal diet and folic acid supplementation to neural tube defect recurrence. Their observations on red cell folate levels support our earlier work,[1] and their conclusions regarding folate supplement point in the same direction as the results of our supplementation study,[2] full details of which will be published shortly.[3] We note that the Cardiff group had methodological problems, as we did. We are puzzled by their use of the term "double-blind" in their more recent paper, which can only have applied until six to nine weeks of gestation, when blood folate levels were estimated and "non-compliers" were identified. The high rate of non-compliance must also have disappointed the authors. We entirely endorse their view that further studies are needed, directed towards the following ends:

(1) To provide further confirmation that vitamin prophylaxis is effective. Our own continuing studies remain encouraging, but among the defects in the offspring of fully "supplemented" women in our second cohort are one recurrence of frank neural tube defect (south-east England); one small, skin-covered lesion without neurological deficit (Northern Ireland); and one very large third fontanelle without involvement of brain or meninges (Yorkshire).

(2) To define further the role of folic acid and other vitamins. We regret that Dr Laurence and his colleagues chose to describe Pregnavite Forte F, a vitamin and iron preparation containing folic acid, as "an expensive blunderbuss preparation." We chose it because our earlier studies[1] demonstrated low first-trimester blood levels of ascorbic acid and riboflavin as well as folic acid in mothers bearing fetuses with central nervous system defects. It is certainly more expensive than folic acid, but should it prove to be more effective the cost (less than 5p daily) would be bearable.

(3) To study carefully mothers who are enrolled for supplementation but who comply only in part. The South Wales "non-compliers" may have complied in part, and details of the two who had recurrences are crucial. It is only from this group that we can discover the minimum effective period of supplementation.

There is considerable urgency. The medical correspondent of *The Times* has advocated (8 May) vitamin supplementation on the basis of our series and those of the Cardiff group. It can no longer be assumed that mothers not given vitamin supplements by research workers necessarily have none. There is also a danger of "do-it-yourself" supplementation by mothers obtaining over-the-counter vitamin preparations, none of which contains folic acid.

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[1] Smithells RW, Sheppard S, Schorah CJ. *Arch Dis Child* 1976;**51**:944-50.
[2] Smithells RW, Sheppard S, Schorah CJ, *et al. Lancet* 1980;i:339-40.
[3] Smithells RW, Sheppard S, Schorah CJ, *et al. Arch Dis Child* (in press).

SIR,—We read with interest the article by Professor K M Laurence and his colleagues (9 May, p 1509) on folate treatment before conception to prevent recurrence of neural-tube defects.

For many years our research group in the University of Aston has been interested in the metabolism of folic acid in mammals, including man. Our results in man[1] show that, in patients receiving a dose of 5 mg of folic acid, the dominant urinary species is unmetabolised folic acid up to 24 hours after the dose. Experiments with mammalian dihydrofolate reductase have shown that folic acid is only a very poor substrate of this enzyme and inhibits the reduction of dihydrofolate with a K_I of 1 μmol/l (A Sahota, personal communication). These results suggest that any folic acid absorbed unchanged from the gut persists unchanged in man for some considerable time. Folic acid itself does not occur naturally, the naturally occurring folates being derivatives of tetrahydrofolic acid. We therefore feel that it is time that the practice of giving folic acid, particularly in large doses, is reviewed. A dose of 4 mg of folic acid would have some inhibitory effect on dihydrofolate reductase.

Additionally, folic acid has been shown to inhibit dihydropteridine reductase[2] a key enzyme in neurotransmitter biosynthesis. This enzyme is missing in some forms of atypical phenylketonuria,[3] with very serious results. The action of folic acid on the developing fetus could therefore be similar to that of aminopterin, a potent inhibitor of dihydrofolate reductase and dihydropteridine reductase, and preparations which contain trimethoprim, which also inhibits these reductases.[2]

We would like to suggest that it would be prudent to avoid any problems that may be caused by folic acid by using a reduced folate such as calcium leucovorin.

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Masked advertising?

SIR,—Dr N Davis (9 May, p 1548) is concerned about drug company sponsorship of a continuing education programme, organised by the Centre for Medical Education at the University of Dundee, where the company's products are mentioned. I would make the following points in reply.

(1) I believe that the pharmaceutical industry does have a role in education of practitioners in the subject areas in which the companies have an interest. Just as clinical trials are done in conjunction with university departments, so also should there be collaboration in the production of educational materials. This is reasonable provided that there is editorial independence. This was the case in this series. The content was based on patients seen in a busy general practice and vetted by a hospital specialist experienced in each of the areas discussed. Reference to drugs was not limited to one company's products.

(2) Therapeutics is an area in which general practitioners express a demand for continuing education. If programmes are to be meaningful and related to day-to-day practice of a general practitioner it is not possible to avoid reference to individual drugs. It is our experience that many general practitioners prefer reference to be made to the trade rather than to the generic names.

(3) Our interest at the Centre for Medical Education is in exploring methods of continuing education in medicine. We have identified some characteristics of programmes which are likely to ensure their success and these are incorporated in the series. The approach seems to be appreciated by many doctors. Of the first 100 doctors replying to a questionnaire we have sent out, 98 expressed a desire to receive a further series and some offered to pay for this. We are at present completing a report evaluating the project in detail.